DOI:10.1111/j.1365-2125.2005.02566.x

Enantioselective disposition of rabeprazole in relation to CYP2C19 genotypes

Masatomo Miura, Hideaki Kagaya, Hitoshi Tada, Tsukasa Uno,[1] Norio Yasui-Furukori,[2] Tomonori Tateishi & Toshio Suzuki[1]

Department of Pharmacy, Akita University Hospital, [1]Department of Clinical Pharmacology and [2]Department of Neuropsychiatry, Hirosaki University School of Medicine, Hirosaki Japan

Correspondence
Toshio Suzuki PhD, Department of Pharmacy, Akita University Hospital, 1-1-1 Hondo, Akita 010–8543, Japan.
Tel: + 81 1 8834 1111
Fax: + 81 1 8836 2628
E-mail: suzuki@hos.akita-u.ac.jp

Keywords
CYP2C19, enantiomer, rabeprazole

Received
17 August 2005
Accepted
20 October 2005
Published *OnlineEarly*
20 December 2005

Aim
Rabeprazole is metabolized to some extent by CYP2C19. The purpose of this study was to elucidate the pharmacokinetics of each rabeprazole enantiomer in three different CYP2C19 genotype groups.

Methods
Twenty-four healthy subjects, of whom each each were homozygous extensive metabolizers (homEMs), heterozygous extensive metabolizers (hetEMs) and poor metabolizers (PMs) for CYP2C19, participated in our study. After a single oral dose of 20 mg of racemic rabeprazole, the plasma concentrations of the rabeprazole enantiomers were measured over the course of 24 h.

Results
The area under the plasma concentration–time curves (AUC) of (*R*)-rabeprazole in homEMs, hetEMs and PMs were 1.8-, 2.2- and 2.4-fold, respectively, greater than those of (*S*)-rabeprazole; the relative AUC ratios of (*R*)- and (*S*)-rabeprazole in homEMs, hetEMs and PMs were 1 : 1.1 : 2.1 and 1 : 0.9 : 1.5, respectively. The mean maximum plasma concentrations (C_{max}) of (*R*)-rabeprazole in homEMs, hetEMs and PMs were 1.7-, 1.9- and 1.8-fold higher, respectively, than those of the corresponding (*S*)-enantiomer ($P < 0.05$). There was no difference between homEMs and PMs in the elimination half-life of (*S*)-rabeprazole, whereas the elimination half-life of (*R*)-rabeprazole was significantly longer in PMs than in homEMs [1.7 h (1.4, 2.0) (mean (95% confidence interval)] *vs.* 0.8 h (0.6, 1.0), respectively, $P < 0.0001$).

Conclusions
(*R*)-Rabeprazole disposition was influenced to a greater degree by CYP2C19 genetic polymorphisms than was that of (*S*)-rabeprazole. The effect of CYP2C19 polymorphisms on the stereoselective disposition of rabeprazole was less than those of lansoprazole and omeprazole.

Introduction

Rabeprazole [[(±)-sodium 2-[[4-methoxypropoxy]-3-methylpyridin-2-yl]-methylsulfinyl]-1*H*-benzimidazole] is a proton pump inhibitor (PPI) that inhibits gastric acid secretion by interacting with (H^+/K^+)-ATPase in gastric parietal cells [1–3]. Rabeprazole is primarily converted non-enzymatically to rabeprazole-thioether, but some is oxidized to demethylated rabeprazole and rabeprazole sulphone by CYP2C19 and CYP3A4, respectively [4–7]. Hence, compared with omeprazole and lansoprazole, CYP2C19 contributes less to the overall metabolism of rabeprazole. Sakai *et al.* have reported that the relative area under the plasma concentration–time curve (AUC) ratios of omeprazole, lansoprazole and rabeprazole in

homozygous extensive metabolizers (homEMs), heterozygous extensive metabolizers (hetEMs) and poor metabolizers (PMs) were 1 : 1.7 : 7.4, 1 : 1.4 : 3.7 and 1 : 1.1 : 1.2, respectively [8]. Similar to other PPIs, rabeprazole also possesses a chiral benzimidazole sulfoxide structure and it has been commercially marketed as a racemic mixture.

In general, the pharmacokinetics of each enantiomer of chiral compounds differs in humans. For lansoprazole, the plasma concentrations of (*R*)-lansoprazole in either healthy subjects or renal transplant recipients are considerably higher than those of the (*S*)-enantiomer after administration of an identical lansoprazole dose [9–11]. (*R*)-Lansoprazole is less influenced by CYP2C19 genetic polymorphisms because CYP2C19-catalysed metabolism is minimal compared with (*S*)-lansoprazole [10, 12]. (*R*)-Lansoprazole is the main active compound. In the case of omeprazole, the plasma concentrations of (*S*)-omeprazole are higher and less influenced by CYP2C19 genetic polymorphisms compared with those of (*R*)-omeprazole and racemic omeprazole [13–15]. This finding has led to the development of esomeprazole, the (*S*)-enantiomer of omeprazole, as the first single enantiomer PPI. We have previously described the kinetic disposition of rabeprazole enantiomers in renal transplant recipients who were CYP2C19 EMs [11]. In that report, the AUCs from 0 to 24 h ($AUC_{0–24}$) and the elimination half-life of (*R*)-rabeprazole were 1.2-fold greater and 1.6-fold longer, respectively, than those of the (*S*)-enantiomer, whereas there was no difference in the maximum plasma concentration (C_{max}) between the two rabeprazole enantiomers. However, no information is available on the effect of CYP2C19 genetic polymorphisms on the enantioselective disposition of rabeprazole.

The aim of this investigation was to elucidate the pharmacokinetics of each enantiomer of rabeprazole among three different CYP2C19 genotype groups (homozygous EMs, heterozygous EMs and PMs) in healthy Japanese subjects.

Materials and methods

Subjects

Healthy Japanese subjects consisted of eight of each CYP2C19 genotype: homEMs, hetEMs and PMs. There were no differences among the three CYP2C19 genotypes in terms of subject profiles, including age (23.4 ± 0.7, 24.1 ± 4.2 and 24.0 ± 1.3 years, respectively), body weight (51.6 ± 7.8, 56.9 ± 9.0 and 55.6 ± 6.5 kg, respectively) and male/female ratios (2 : 6, 6 : 2 and 3 : 5, respectively). None of the subjects had a history of significant medical illness or hypersensitivity to any drug and none was a smoker. Furthermore, they were not allowed to take drugs or medications during the study periods. The study protocol was approved by the Ethics Committee of Akita University Hospital and Hirosaki University Hospital, and all subjects gave their written informed consent before participating.

Study protocols

Each subject received a single oral dose of 20 mg of rabeprazole sodium (Pariet®; Eisai, Tokyo, Japan) with a glass of tap water at 09.00 h. Venous blood samples used to determine the plasma concentration of rabeprazole enantiomers were taken before and 1, 2, 3, 4, 5, 6, 8, 10, 12 and 24 h after dosing. The samples were centrifuged at 3000 *g* immediately after collection and stored at −80 °C until analysis. All subjects fasted for 10 h before the administration of rabeprazole and had a standard meal 4 h later. Alcohol and caffeinated beverages were forbidden during the test period.

CYP2C19 genotyping

The genotyping procedure used to identify the CYP2C19 wild-type gene and its two mutant alleles, CYP2C19*2 in exon 5 and CYP2C19*3 in exon 4, was a polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method [16]. CYP2C19 genotype analysis revealed four different patterns as follows: **1/*1* in eight, **1/*2* in five, **1/*3* in three and **2/*2* in eight subjects. Individuals with these genotype patterns were divided into three groups; homEMs (**1/*1*, $n = 8$); hetEMs (**1/*2* and **1/*3*, $n = 8$); and PMs (**2/*2*, $n = 8$).

Reagents and chemicals

Rabeprazole enantiomers and omeprazole-thioether were donated from Eisai Co. Ltd.. An Oasis HLB extraction cartridge was purchased from Waters (Milford, MA, USA). All solvents used were of high-performance liquid chromatogrphy (HPLC) grade (Wako Pure Chemical Industries, Osaka, Japan) and all other reagents and chemicals were purchased from either Wako Chemical Industries or Nacalai Tesque (Kyoto, Japan).

Analysis of rabeprazole enantiomers in plasma

The plasma concentrations of rabeprazole enantiomers were determined according to the HPLC method of Miura *et al.* [11]. Briefly, omeprazole-thioether (20 ng) in methanol (10 µl) was added to the samples (100 µl) as an internal standard, then the samples were diluted with water (1.0 ml) and the solutions were mixed for a short time. Each mixture was applied to an Oasis HLB extraction cartridge that had been previously activated

with methanol and water (1.0 ml each). The cartridges were then washed with 60% methanol in water (1.0 ml), followed by elution with 100% methanol (1.0 ml). The eluates were evaporated to dryness in a vacuum at 60°C by a rotary evaporator (Iwaki, Tokyo, Japan). The residues were dissolved in 50 µl of methanol and 50 µl of the mobile phase, and each aliquot (50 µl) was injected into the HPLC apparatus. The HPLC column used was a Chiral CD-Ph (250 × 4.6 mm i.d.; Shiseido Co. Ltd, Tokyo, Japan). The mobile phase consisted of 0.5 M $NaClO_4$-acetonitrile (60 : 40, v/v), which was degassed in an ultrasonic bath prior to use. A flow rate of 0.5 ml min^{-1} was used at ambient temperature, with the wavelength set at 285 nm. The lower limit of quantification for this assay was 5.0 ng ml^{-1} for each rabeprazole enantiomer. The coefficient of variation of inter- and intraday assays was <7.8% and the accuracy was within 4.7% for both analytes at concentrations of 5, 50, 250, 500 and 1000 ng ml^{-1}.

Pharmacokinetic analysis

Pharmacokinetic analysis of the rabeprazole enantiomers was carried out by a standard noncompartmental method using WinNonlin (Pharsight Co., Mountain View, CA, USA; version 4.0.1). The elimination half-life was obtained by log-linear regression of the terminal phase of the concentration–time data with at least three sampling points (elimination half-life = ln2/*ke*; *ke* = elimination rate constant). The total area under the observed plasma concentration–time curve (AUC) was calculated using the linear trapezoidal rule. Extrapolation of AUC from the last measurable concentration (C_t) to infinity ($AUC_{t-\infty}$) was performed by adding the value C_t/ke (where C_t = plasma concentration for t hours after rabeprazole administration). The maximum plasma concentration (C_{max}) and time required to reach the C_{max} (t_{max}) were obtained directly from the profile.

Statistical analysis

All results are expressed as mean values ± standard deviation and 95% confidence intervals (CI). Statistical comparisons of the parameters were supplemented with the multiple comparison procedure of Scheffe using StatView software (SAS Institute, Cary, NC, USA; version 5.0). A P-value of <0.05 was considered to be statistically significant.

The necessary sample size was calculated using the following assumption. The AUC, C_{max} and elimination half-life for rabeprazole are of the same proportion between the EMs and the PMs, as reported in the literature ($n = 6$ each) [17], and so six subjects are necessary for each genotype with $\alpha = 0.05$ and $\beta = 0.2$ (power of 80%). To allow for stratification by genotype, eight subjects for each group were targeted for enrolment in this study. This analysis was performed with S-PLUS (Mathematical System Inc, Tokyo, Japan; version 6.0).

Results

The mean plasma concentrations of (*R*)-rabeprazole were much higher than those of (*S*)-rabeprazole in all three CYP2C19 genotype groups (Figure 1, Table 1). The AUCs of (*R*)-rabeprazole in homEMs, hetEMs and PMs were 1.8- (1.4, 2.1) [mean (95% CI)] ($P < 0.05$), 2.2- (2.0, 2.4) ($P < 0.005$) and 2.4-fold (2.1, 2.7) ($P < 0.0001$) higher, respectively, than those of the corresponding (*S*)-enantiomer. The relative AUC ratios of (*R*)- and (*S*)-enantiomer in homEMs, hetEMs and PMs were 1 : 1.1 : 2.1 and 1 : 0.9 : 1.5, respectively. The mean maximum plasma concentrations (C_{max}) of (*R*)-rabeprazole in homEMs, hetEMs and PMs were 1.7- (1.5, 2.0) ($P < 0.05$), 1.9- (1.7, 2.0) ($P < 0.05$) and 1.8-fold (1.3, 2.3) ($P < 0.005$) higher, respectively, than those of the corresponding (*S*)-enantiomer. However, there were no significant differences for the mean C_{max} values of (*R*)- or (*S*)-rabeprazole across the three CYP2C19 genotype groups. In contrast, although there was no difference in the elimination half-life of (*S*)-rabeprazole across the three different CYP2C19 genotype groups, the elimination half-life of (*R*)-rabeprazole was significantly longer in PMs than in homEMs ($P < 0.0001$).

Discussion

In the present study, we examined the pharmacokinetics of rabeprazole enantiomers in relation to CYP2C19 genotype status by administering 20 mg of racemic rabeprazole to healthy Japanese subjects. We found no statistically significant differences in the pharmacokinetics of (*S*)-rabeprazole between homEMs and PMs. However, our results showed that the pharmacokinetics of (*R*)-rabeprazole were more intensely affected by CYP2C19 polymorphisms than those of the (*S*)-enantiomer. The elimination half-life of (*R*)-rabeprazole in PMs was significantly longer than in homEMs ($P < 0.0001$), whereas there was no significant difference in C_{max} value between homEMs and PMs ($P = 0.0721$). A power analysis based on the observed differences revealed that more than six subjects of each genotype would have been necessary to demonstrate statistical significance with a power of 0.8. The power between homEMs and PMs calculated from our present data, which consisted of eight of each genotype, was 0.478 for the C_{max} value of (*R*)-rabeprazole and 0.677 and 0.665, respectively, for the AUC and C_{max} of (*S*)-

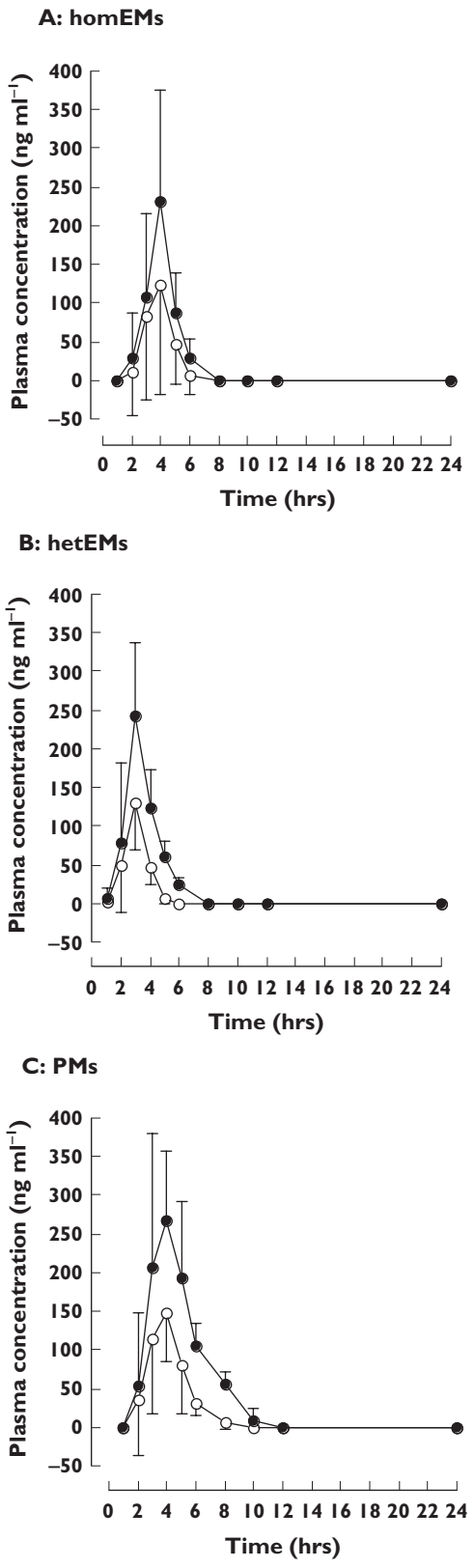

Figure 1

Mean ± SD plasma concentration–time profiles of (*R*)-rabeprazole (●) and (*S*)-rabeprazole (○) for A: homozygous extensive metabolizers (EMs); B: heterozygous EMs; and C: poor metabolizers, after a 20-mg oral dose of racemic rabeprazole

rabeprazole. In the present study, there was no CYP2C19-specific genetic effect on the first-pass metabolism of either rabeprazole enantiomer.

In CYP2C19 EMs, the C_{max} of (*R*)-rabeprazole was significantly higher than that of the (*S*)-enantiomer ($P < 0.05$), but the elimination half-life did not differ for the two enantiomers. On the other hand, in CYP2C19 PMs, the C_{max} and the elimination half-life of (*R*)-rabeprazole were significantly higher and longer, respectively, than those of the (*S*)-enantiomer ($P < 0.005$ and $P < 0.0001$, respectively). Racemic rabeprazole has a low oral bioavailability of about 52% because of extensive first-pass metabolism [18]. Instability of (*S*)-rabeprazole in the human body seems to cause the low bioavailability of racemic rabeprazole. The significant difference in C_{max} between the rabeprazole enantiomers may be due to the stereoselective reduction of (*S*)-rabeprazole into rabeprazole thioether by non-enzymatic means, or stereoselective oxidation into rabeprazole sulphone by CYP3A4. However, no information is available about the stereoselective properties of rabeprazole metabolism from *in vitro* studies with human liver microsomes. The AUC ratios for (*R*)-rabeprazole to (*S*)-rabeprazole in homEMs, hetEMs and PMs were 1.8, 2.2 and 2.4, respectively. Hence, the *R/S* ratio for the AUC in PMs was 1.3-fold higher than in homEMs ($P < 0.05$).

The degree to which CYP2C19 participates in the overall metabolism of rabeprazole has been reported to be much less compared with that of lansoprazole and omeprazole [5, 8, 19, 20]. The *R/S* ratios for the AUC of lansoprazole in homEMs, hetEMs and PMs are 12.7, 8.5 and 5.8, respectively [10], and the *R/S* ratios for the AUC of omeprazole in EMs and PMs are 0.5 and 1.7, respectively [13]. Thus, in comparison with lansoprazole and omeprazole, the enantioselective disposition of rabeprazole is less affected by CYP2C19 genetic polymorphisms.

The pharmacokinetics of rabeprazole enantiomers in the present study using healthy CYP2C19 EM subjects differed from those reported in CYP2C19 EM renal transplant recipients receiving tacrolimus [11]. The mean C_{max} values of (*S*)-rabeprazole are higher and the elimination half-life of (*R*)-rabeprazole is longer in renal transplant recipients on tacrolimus, a substrate of CYP3A4 [21, 22], than in our present study's healthy subjects. CYP3A4 is also the high-affinity enzyme responsible for rabeprazole sulphone formation. Further studies may be needed to elucidate the interactions between rabeprazole and tacrolimus.

The difference in the pharmacological activity between (*R*)- and (*S*)-rabeprazole has not yet been estab-

Table 1
Pharmacokinetic parameters of (*R*)- and (*S*)-rabeprazole in three CYP2C19 genotype groups

Study group	Homozygous EMs	Heterozygous EMs	PMs
(R)-*Rabeprazole*			
C_{max} (ng ml^{-1})	257 ±116	279 ±76	330 ±97
(95% CI)	(160, 354)	(200, 332)	(282, 425)
t_{max} (h)	3.6 ±0.7	2.9 ±0.4	3.5 ±0.9
(95% CI)	(3.0, 4.3)	(2.6, 3.2)	(2.7, 4.3)
Half-life (h)	0.8 ±0.2***	0.9 ±0.2***	1.7 ±0.4
(95% CI)	(0.6, 1.0)	(0.8, 1.0)	(1.4, 2.0)
$AUC_{0-\infty}$ (ng h^{-1} ml^{-1})	514 ±258***	573 ±75***	1068 ±212
(95% CI)	(299, 730)	(484, 627)	(891, 1245)
(S)-*Rabeprazole*			
C_{max} (ng ml^{-1})	145 ±50†	153 ±51†	201 ±44††
(95% CI)	(103, 186)	(109, 197)	(164, 237)
t_{max} (h)	3.5 ±0.8	2.8 ±0.5	3.5 ±0.8
(95% CI)	(2.9, 4.1)	(2.4, 3.1)	(2.9, 4.1)
Half-life (h)	0.8 ±0.3	0.7 ±0.2	1.0 ±0.1†††
(95% CI)	(0.6, 1.1)	(0.5, 0.9)	(0.9, 1.1)
$AUC_{0-\infty}$ (ng h^{-1} ml^{-1})	294 ±154†	260 ±49*††	445 ±88†††
(95% CI)	(166, 422)	(213, 307)	(372, 519)
R/S			
C_{max}	1.7 ±0.3	1.9 ±0.2	1.8 ±0.2
(95% CI)	(1.5, 2.0)	(1.7, 2.0)	(1.3, 2.3)
$AUC_{0-\infty}$	1.8 ±0.4*	2.2 ±0.3	2.4 ±0.4
(95% CI)	(1.4 ±2.1)	(2.0 ±2.4)	(2.1 ±2.7)

*The values are shown as the mean ± SD. Cmax, Maximum plasma concentration; tmax, time to reach Cmax; $AUC_{0-\infty}$, area under the plasma concentration–time curve from 0 to infinity; EM, extensive metabolizer; PM, poor metabolizer. *P < 0.05; ***P < 0.0001 compared with the PM group; †P < 0.05; ††P < 0.005; †††P < 0.0001 compared with (R)-rabeprazole.*

lished. Therefore, it is difficult to evaluate clinical outcomes based on our results. Even if the pharmacological activity of racemic rabeprazole is predominantly mediated by one enantiomer, the pharmacodynamics of each rabeprazole enantiomer would be less affected by CYP2C19-related genetic differences compared with omeprazole and lansoprazole. Especially in the case of (*S*)-rabeprazole, the influence of CYP2C19 polymorphisms is likely to be small.

In conclusion, the present study indicates that the plasma concentrations and the degree of CYP2C19-mediated metabolism of (*R*)-rabeprazole are higher and greater, respectively, than those of the (*S*)-enantiomer. However, the *R*/*S* ratios for the AUC of rabeprazole in homEMs, hetEMs and PMs are 1.8, 2.2 and 2.4, respectively, suggesting a lesser effect of CYP2C19 polymorphisms on the stereoselective disposition of rabeprazole compared with lansoprazole and omeprazole.

We thank Eisai Co. Ltd. (Tokyo, Japan) for providing the rabeprazole enantiomers. This work was supported by a grant (no.17923061) from the Japan Society for the Promotion of Science, Tokyo, Japan.

References

1 Prakash A, Faulds D. Rabeprazole. Drugs 1998; 55: 261–7.
2 Morii M, Takata H, Fujisaki H, Takeguchi N. The potency of substituted benzimidazoles such as E3810, omeprazole, Ro 18-5364 to inhibit gastric H+, K(+)-ATPase is correlated with the rate of acid-activation of the inhibitor. Biochem Pharmacol 1990; 39: 661–7.
3 Fujisaki H, Shibata H, Oketani K, Murakami M, Fujimoto M, Wakabayashi T, Yamatsu I, Yamaguchi M, Sakai H, Takeguchi N. Inhibitions of acid secretion by E3810 and omeprazole, and their reversal by glutathione. Biochem Pharmacol 1991; 42: 321–8.
4 Ishizaki T, Horai Y. Review article: cytochrome P450 and the metabolism of proton pump inhibitors — emphasis on rabeprazole. Aliment Pharmacol Ther 1999; 13: 27–36.

5 Yasuda S, Horai Y, Tomono Y, Nakai H, Yamato C, Manabe K, Kobayashi K, Chiba K, Ishizaki T. Comparison of the kinetic disposition and metabolism of E3810, a new proton pump inhibitor, and omeprazole in relation to S-mephenytoin 4′-hydroxylation status. Clin Pharmacol Ther 1995; 58: 143–54.

6 VandenBranden M, Ring BJ, Binkley SN, Wrighton SA. Interaction of human liver cytochromes P450 in vitro with LY307640, a gastric proton pump inhibitor. Pharmacogenetics 1996; 6: 81–91.

7 Klotz U. Pharmacokinetic considerations in the eradication of Helicobacter pylori. Clin Pharmacokinet 2000; 38: 243–70.

8 Sakai T, Aoyama N, Kita T, Sakaeda T, Nishiguchi K, Nishitora Y, Hohda T, Sirasaka D, Tamura T, Tanigawara Y, Kasuga M, Okumura K. CYP2C19 genotype and pharmacokinetics of three proton pump inhibitors in healthy subjects. Pharm Res 2001; 18: 721–7.

9 Kim KA, Shon JH, Park JY, Yoon YR, Kim MJ, Yun DH, Kim MK, Cha IJ, Hyun MH, Shin JG. Enantioselective disposition of lansoprazole in extensive and poor metabolizers of CYP2C19. Clin Pharmacol Ther 2002; 72: 90–9.

10 Miura M, Tada H, Yasui-Furukori N, Uno T, Sugawara K, Tateishi T, Suzuki T. Pharmacokinetic differences between the enantiomers of lansoprazole and its metabolite, 5-hydroxylansoprazole, in relation to CYP2C19 genotypes. Eur J Clin Pharmacol 2004; 60: 623–8.

11 Miura M, Kagaya H, Tada H, Sagae Y, Satoh S, Habuchi T, Suzuki T. Comparison of enantioselective disposition of rabeprazole versus lansoprazole in renal transplant recipients who are CYP2C19 extensive metabolizers. Xenobiotica 2005; 35: 479–86.

12 Miura M, Tada H, Yasui-Furukori N, Uno T, Sugawara K, Tateishi T, Suzuki T. Enantioselective disposition of lansoprazole in relation to CYP2C19 genotypes in the presence of fluvoxamine. Br J Clin Pharmacol 2005; 60: 61–8.

13 Andersson T, Hassan-Alin M, Hasselgren G, Rohss K, Weidolf L. Pharmacokinetic studies with esomeprazole, the (S)-isomer of omeprazole. Clin Pharmacokinet 2001; 40: 411–26.

14 Kanazawa H, Okada A, Higaki M, Yokota H, Mashige F, Nakahara K. Stereospecific analysis of omeprazole in human plasma as a probe for CYP2C19 phenotype. J Pharm Biomed Anal 2003; 30: 1817–24.

15 Tybring G, Bottiger Y, Widen J, Bertilsson L. Enantioselective hydroxylation of omeprazole catalyzed by CYP2C19 in Swedish white subjects. Clin Pharmacol Ther 1997; 62: 129–37.

16 De Morais SM, Wilkinson GR, Blaisdell J, Meyer UA, Nakamura K, Goldstein JA. Identification of a new genetic defect responsible for the polymorphism of (*S*)-mephenytoin metabolism in Japanese. Mol Pharmacol 1994; 46: 594–8.

17 Horai Y, Kimura M, Furuie H, Matsuguma K, Irie S, Koga Y, Nagahama T, Murakami M, Matsui T, Yao T, Urae A, Ishizaki T. Pharmacodynamic effects and kinetic disposition of rabeprazole in relation to CYP2C19 genotypes. Aliment Pharmacol Ther 2001; 15: 793–803.

18 Sclar DA, Tartaglione TA, Fine MJ. Overview of issues related to medical compliance with implications for the outpatient management of infectious diseases. Infect Agents Dis 1994; 3: 266–73.

19 Ishizaki T, Horai Y. Review article: cytochrome P450 and the metabolism of proton pump inhibitors — emphasis on rabeprazole. Aliment Pharmacol Ther 1999; 3: 27–36.

20 Desta Z, Zhao X, Shin JG, Flockhart DA. Clinical significance of the cytochrome P450 2C19 genetic polymorphism. Clin Pharmacokinet 2002; 41: 913–58.

21 Sattler M, Guengerich FP, Yun CH, Christians U, Sewing KF. Cytochrome P-450 3A enzymes are responsible for biotransformation of FK506 and rapamycin in man and rat. Drug Metab Dispos 1992; 20: 753–61.

22 Shiraga T, Matsuda H, Nagase K, Iwasaki K, Noda K, Yamazaki H, Shimada T, Funae Y. Metabolism of FK506, a potent immunosuppressive agent, by cytochrome P450 3A enzymes in rat, dog and human liver microsomes. Biochem Pharmacol 1994, 47: 727–35.